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**UNITED STATES ARMY
ENVIRONMENTAL HYGIENE
AGENCY**

ABERDEEN PROVING GROUND, MD 21010-5422

SKIN SENSITIZATION OF THE INSECTICIDE PERMETHRIN IN MAN
AND THE POTENTIAL FOR NONIMMUNOLOGICAL CONTACT URTICARIA
STUDY NO. 75-51-0351-86
SEPTEMBER 1984 - DECEMBER 1985

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Animals	Man	Skin															
Guinea pig	Nonimmunological contact urticaria																
Human	Patch test																
Insecticide	Permethrin																
Irritation	Sensitization																
20. ABSTRACT (Continue on reverse side if necessary and identify by block number) <p>The insecticide permethrin was tested in man for skin irritation and sensitization using the prophetic patch test. The potential for nonimmunological contact urticaria was also tested using the guinea pig as the predictive model. The results of both tests were negative. It is recommended that permethrin be approved for further evaluation in man as a clothing impregnant at concentrations of 0.125 mg/cm², or less, but that subjects be closely monitored for adverse skin effects.</p>																	

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U. S. ARMY ENVIRONMENTAL HYGIENE AGENCY
ABERDEEN PROVING GROUND, MARYLAND 21010-5422

REPLY TO
ATTENTION OF

HSHB-OT

13 June 1986

SUBJECT: Skin Sensitization of the Insecticide Permethrin in Man and the Potential for Nonimmunological Contact Urticaria, Study No. 75-51-0351-86, September 1984 - December 1985

Executive Director
Armed Forces Pest Management
Forest Glen Section, WRAMC
Washington, DC 20307-5001

EXECUTIVE SUMMARY

The purpose and a summary of the recommendations of the enclosed report follow:

a. Purpose. To determine the skin irritation and sensitization of the insecticide permethrin in man, and the potential for nonimmunological contact urticaria (NICU) using the guinea pig as the predictive model.

b. Recommendations. Based on good preventive medicine practices, it is recommended that the insecticide permethrin be approved for further evaluation in man as a clothing impregnant at a concentration of 0.125 mg/cm², or less. Personnel wearing permethrin-treated clothing during controlled field trials should be closely monitored for signs and symptoms of adverse skin effects.

FOR THE COMMANDER:

Encl

for [Signature]
N. Joe Thompson
Colonel, MC
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Environmental Health



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DEPARTMENT OF THE ARMY
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REPLY TO
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HSHB-OT

SKIN SENSITIZATION OF THE INSECTICIDE PERMETHRIN IN MAN
AND THE POTENTIAL FOR NONIMMUNOLOGICAL CONTACT URTICARIA
STUDY NO. 75-51-0351-86
SEPTEMBER 1984 - DECEMBER 1985

1. AUTHORITY.

a. Memorandum of Understanding between the US Army Environmental Hygiene Agency; the US Army Health Services Command; the Department of the Army, Office of the Surgeon General; the Armed Forces Pest Control Board; and the US Department of Agriculture; Agricultural Research, Science and Education Administration; titled Coordination of Biological and Toxicological Testing of Pesticides, effective 23 January 1979.

b. Letter, AFPCB, Armed Forces Pest Control Board, 21 October 1975, subject: Request for Toxicological Evaluation.

c. Letter, AFPCB, Armed Forces Pest Control Board, 5 April 1977, subject: Request for Toxicological Evaluation

2. REFERENCES.

a. Marzulli, F. and H. Maibach, "Contact Allergy: Predictive Testing in Man", Advances in Modern Toxicology, 4:353-372, 1977.

b. Lahti, A. and H. Maibach, "An Animal Model for Nonimmunological Contact Urticaria" Toxicol. Appl. Pharmacol., (in press)

3. PURPOSE. To determine the skin irritation and sensitization of the insecticide permethrin in man, and the potential for nonimmunological contact urticaria (NICU) using the guinea pig as the predictive model.

4. BACKGROUND. The Armed Forces Pest Management Board (AFPMB) is recommending the use of permethrin as a clothing impregnant against medically important arthropods during contingency operations. An impregnation rate of 0.125 mg/cm² is considered efficacious and is without toxicological effects in animals. However, the obvious potential for intimate skin contact in man necessitates a more indepth health effects evaluation of the insecticide, particularly towards skin irritation and sensitization. Accordingly, two contracted studies* were performed. The

* Contract No. DAAD05-84-M-M341 (both), Howard I. Maibach, M.D., Dept of Dermatology, University of California Medical Center, San Francisco, CA 94143

first was a prophetic patch test in humans to forecast the allergenic potential of permethrin. The second, a recently developed predictive procedure using animals, measured the potential for nonimmunological contact urticaria (NICU), an immediate allergic reaction. Collectively, the data will provide a basis for the continued development of permethrin as a military clothing impregnant and support the data base requirements for regulatory acceptance.

5. TEST MATERIALS.

a. Technical Permethrin, 92.5 percent. Permethrin is identified by CAS registry no. 52645-53-1.

b. Ethyl alcohol, 95 percent, was used as the permethrin diluent in the human tests. In the animal assay, reagent grade acetone was the diluent.

6. TEST SUBJECTS.

a. Prophetic Patch Test. The test panel included 184 adult subjects as described in Table 1. They were examined prior to the commencement of the study and deemed to be free of any active skin pathology. Medical histories and consent forms were obtained from all subjects. Male and female panelists ranged in ages from 18 to 80 and represented 3 races.

TABLE 1. PROPHETIC PATCH TEST PANEL ACCORDING TO AGE, SEX, AND RACE.
(Percent of Subjects)

Age Group	M/B	M/W	M/O	F/B	F/W	F/O	F/A
18 - 25	1.1	3.8	---	1.1	8.7	---	---
26 - 35	1.1	6.6	---	3.3	14.8	---	0.5
36 - 50	---	6.6	---	2.7	10.4	---	---
51 - 65	---	6.6	1.1	3.2	13.7	0.5	---
> 65	1.6	3.8	---	2.2	6.6	---	---

M - Male F - Female B - Black W - White O - Oriental A - Asian

b. NICU Assay. Twelve Hartley strain guinea pigs were used. Two animals were later rejected because their earlobes, the site of permethrin application, were judged unsuitable for testing. Animals were supplied a commercial laboratory diet and water ad libitum.

7. METHODS.

a. Prophetic Patch Test. The human patch testing was a modification of the procedure set forth by Draize (reference 2a). The test patches (Webril) were moistened with about 0.2 mL of a 40 percent permethrin solution and secured to the skin by means of an occlusive bandage (Blenderm® tape). The test site was the upper arm or back for each subject. During the sensitization (induction) period, the first 3 weeks, patches were applied thrice weekly. The panelists were instructed to leave the patches on, including weekends, and keep them dry following each application. All applications were made to the same site and observations made at each patch change. Two weeks after the sensitization period, the challenge or elicitation application was made to a previously unpatched site. The challenge patches were removed 72 hours later and scored at 96 hours. The scoring scale employed for all evaluations was as follows:

- I = minimal glazing, such as in the "peau d'orange"
- 0 = negative
- + = equivocal reaction
- +1 = erythema
- +2 = erythema and induration
- +3 = erythema, induration and vesicles
- +4 = erythema, induration and bullae

b. NICU Assay. The contact urticaria procedure followed the method of Lahti and Maibach (reference 2b). Briefly, this involved the application of 0.1 mL of a 25 percent permethrin solution in acetone to the right earlobe of each guinea pig, 0.05 mL to each side. Acetone only was applied to the left ear (vehicle control). A string micrometer was used to measure the earlobe thickness, before and at timed intervals for up to 3 hours after application of the test material. An increase in lobe thickness, compared to the acetone control ear, was the index for allergic response.

8. RESULTS.

a. Prophetic Patch Test. A summary of the prophetic patch test results appears as Table 2. Quoting from the contractor's final report, "There was no evidence of the induction of allergic contact dermatitis to this [permethrin] sample. Several subjects noted transient burning, stinging, and/or itching. For this reason, it may be appropriate to assay for contact urticaria and subjective irritation."

b. NICU Assay. The results of the contact urticaria assay in guinea pigs appears as Table 3. The contractor concluded, "There was no evidence of the production of contact urticaria with these [permethrin] samples."

®Blenderm is a registered tradename of 3M Company, St. Paul, Minnesota. Use of trademarked name does not imply endorsement by the US Army, but is intended only to assist in identification of a specific product.

TABLE 2. SUMMARY OF PROPHETIC PATCH TEST RESULTS WITH PERMETHRIN.

Summary of response to site No. 1.
 Permethrin: 400 mg/mL in 95% alcohol
 Number of subjects: 210
 Number not completing study: 26

Grade	Induction Application									Elicitation	
	1	2	3	4	5	6	7	8	9	72 hr	96 hr
0	203	199	196	194	191	189	187	187	187	0	0
±	0	0	0	0	0	0	0	0	0	0	0
+1	0	0	0	0	0	0	0	0	0	0	0
+2	0	0	0	0	0	0	0	0	0	0	0
+3	0	0	0	0	0	0	0	0	0	0	0
+4	0	0	0	0	0	0	0	0	0	0	0
Total	203	199	196	194	191	189	187	187	187	184	184

9. DISCUSSION.

a. Permethrin has undergone extensive toxicological evaluation in this laboratory and others. To date, there has been no basis for suspecting that the insecticide, when impregnated in military fabrics at a rate of 0.125 mg/cm², should cause adverse health effects in man. The results of the current studies support this view. The prophetic patch test used 80 mg of permethrin under an occlusive patch for each application, about the quantity expected in a 16 x 16 inch piece of impregnated fabric. In the animal test for contact urticaria, a single application of about 31 mg of insecticide was made to the earlobe, equivalent to a 10 x 10 inch swatch of treated cloth. While neither test was intended to mimic a projected human dose, each was certainly sufficient to illicit irritation, sensitization, or an immediate allergic response in sensitive individuals, particularly, given the concentrated area of application.

b. The prophetic patch test performed in man in this study is a valuable predictive tool, but is not without limitations. The mathematical considerations involved in extrapolating to large populations are complex. For example, there may be no skin reactions in a test population of 200 subjects, yet as many as 15 of every 1000 of the general population

TABLE 3. RESULTS OF THE NONIMMUNOLOGICAL CONTACT URTICARIA (NICU) ASSAY

Time Minutes	Ear Cont/Test	Ear Width* mm	S.D.	No. Positive Reactions
0	C	1.13	0.126	-
	T	1.11	0.089	
15	C	1.18	0.166	0
	T	1.17	0.081	
30	C	1.13	0.115	0
	T	1.14	0.077	
45	C	1.22	0.258	0
	T	1.16	0.075	
60	C	1.12	0.090	0
	T	1.13	0.040	
75	C	1.12	0.090	0
	T	1.14	0.060	
90	C	1.13	0.081	0
	T	1.16	0.057	
105	C	1.13	0.101	0
	T	1.15	0.039	
120	C	1.12	0.109	0
	T	1.16	0.044	
135	C	1.13	0.094	0
	T	1.15	0.044	
150	C	1.13	0.086	0
	T	1.15	0.037	
165	C	1.13	0.077	0
	T	1.14	0.037	
180	C	1.13	0.087	0
	T	1.15	0.041	

* Mean of 10 animals; two measurements per ear.
S.D. - Standard Deviation

may react (95 percent confidence)*. This predictive variability stems from a large number of factors likely to effect skin sensitization in the field. These include the skin site, climatic conditions, area and frequency of application, and others. This is not to suggest that the subject test should be viewed with suspicion, but rather indicates a continued need for monitoring personnel for adverse skin reactions during field trials.

c. In support of the reported patch test in humans is the wide age variability of the panelists (18 - 80). While representative of the general population, it also predisposed the panel to subjects likely to react to offensive topical chemicals, particularly the elderly. Conversely, a military population, being younger and in generally better health, should be less susceptible to allergenic reactivity.

d. The transient symptoms reported by the patch test subjects, i.e., burning and itching, were not substantiated by an observable skin reaction. Further, neither contact urticaria nor subjective irritation was noted in the followup NICU assay in guinea pigs. The absence of observable skin effects are important from a health effects standpoint but may be negated if personnel are reluctant to wear the treated uniform because of perceived discomfort. Hopefully, the symptomatic effects will not be perpetuated in those wearing impregnated clothing as opposed to an occlusive test patch.

10. CONCLUSIONS. The insecticide permethrin should cause neither skin irritation nor sensitization in man following multiple exposures to permethrin-impregnated military fabrics. An immediate allergic reaction to permethrin skin contact is not anticipated in man, based on the results of a predictive animal assay.

11. RECOMMENDATIONS. Based on good preventive medicine practices, it is recommended that the insecticide permethrin be approved for further evaluation in man as a clothing impregnant at a concentration of 0.125 mg/cm² or less. Personnel wearing permethrin-treated clothing during controlled field trials should be closely monitored for signs and symptoms of adverse skin effects.



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*Henderson, C.R. and E.C. Riley, "Certain Statistical Considerations in Patch Testing," J. Invest. Dermatol. 6:227-232 (1945)